**#C91 Association of O6-methylguanine-DNA methyltransferase Ile143Val variant allele with reduced risk of colorectal cancer in women.** Gregory J. Tranah,[1] James Bugni,[2] Leona Samson,[2] Edward Giovannucci,[1] Jing Ma,[3] Charles Fuchs,[3] David J. Hunter.[3] Harvard School of Public Health,[1] Boston, MA, Massachusetts Institute of Technology,[2] Cambridge, MA, Channing Laboratory,[3] Boston, MA.

O6-methylguanine-DNA methyltransferase (MGMT) removes mutagenic adducts from the O6-guanine base residue in DNA. Unrepaired O6-methylguanine results in G:C to A:T transitions, which are commonly observed in mutated K-ras oncogenes in colorectal tumors. O6-methylguanine adducts arise from exposure to alkylating substances derived from tobacco smoke, occupation and diet. MGMT silencing by promoter hypermethylation occurs in many primary tumors and such silencing may cause increased G:C to A:T transitions in K-ras oncogenes in colorectal tumors. In addition, MGMT activity is inhibited by the ethanol metabolite, acetaldehyde. After DNA repair, MGMT is thought to switch to a transcriptional suppressor that inhibits estrogen receptor (ER) mediated cell proliferation. If true, in addition to the direct repair of O6-methylguanine adducts MGMT may indirectly protect ER-regulated cells from O6-guanine-directed mutations during replication. Three common non-synonymous MGMT coding region variants, Leu84Phe and genetically linked Ile143Val and Lys178Arg have been reported. A 3- dimensional MGMT structural model shows that the Leu84 and Ile143 residues lie in close proximity to a conserved estrogen receptor interacting helix although the effect of these variant alleles on the regulation of estrogen receptor-mediated cell proliferation is unknown. We assessed the association between Leu84Phe and Ile143Val polymorphisms and risk of colorectal cancer in a case-control study (197 cases and 2500 controls) nested in the Nurses' Health Study (NHS) and hypothesize that these polymorphisms modify risk of colorectal cancer associated with smoking, postmenopausal hormone use, and intake of alcohol. Women carrying one or two copies of the variant 143Val allele had a significant 50% lower risk of colorectal cancer compared with those carrying the homozygous 143Ile genotype [odds ratio (OR) = 0.52, 95% confidence interval (CI) 0.34-0.81]. In addition, individuals who were carriers of the variant 143Val allele and current users of postmenopausal hormones had a significant 80% lower risk of colorectal cancer (OR = 0.22, 95% CI 0.10-0.52) relative to women that were homozygous for the common Ile143 allele and never or past users of postmenopausal hormones (P interaction = 0.006). Although the Leu84Phe polymorphism was not directly associated with risk of colorectal cancer in our study, we observed a statistically significant interaction between alcohol intake and the Leu84Phe polymorphism (P interaction = 0.003). Among women who drank <7.5 gm/day of alcohol, carrying one or two copies of the variant 84Phe allele was associated with a significant 46% lower risk compared with homozygous 84Leu (OR = 0.54, 95% CI 0.31-0.95). However, among those who drank >=7.5 gm/day of alcohol, 84Phe allele carrier status was associated with a significantly increased risk (OR = 1.94, 95% CI 1.00 -3.78). Overall, our results are consistent with previous studies that suggest that women who are current users of postmenopausal hormones are at reduced risk of colorectal cancer. The results observed in this study may suggest that MGMT influences the risk of colorectal cancer through ER-mediated cell proliferation, which occurs in response to DNA alkylation damage.

**#C92 Rare *ATM* genetic variants and breast cancer risk in the U.S. Radiologic Technologist Study.** Jeffery P. Struewing,[1] Denise L. Stredrick,[1] Michele M. Doody,[2] Alice J. Sigurdson.[2] Laboratory of Population Genetics, National Cancer Institute, National Institutes of Health,[1] Bethesda, MD, Radiation Epidemiology Branch, National Cancer Institute, National Institutes of Health,[2] Bethesda, MD.

Ataxia telangiectasia (AT) is a rare autosomal recessive disease caused by mutations (commonly protein-truncating) in the large *ATM* gene and breast cancer is more common in female relatives of AT patients. The numerous mutations that cause AT are individually rare, and no breast cancer study has been large enough to identify a significant excess of AT-related mutations. It is unclear whether missense mutations in *ATM* may also contribute to breast cancer risk. We are studying 16 nucleotide variants in *ATM* with individual Taqman and dHPLC assays in a breast cancer case-control study nested in a cohort study of U.S. radiologic technologists. Variants selected for study include AT-causing protein-truncating and splicing variants identified in multiple ethnic groups (IVS10-6T>G, 1563delAG, K1192K, 3802delG, IVS62+1G>A, R3047X) and/or shown to alter ATM function (7636del9, S2592C), non-conservative missense mutations (S49C, S707P, F858L, P1054R, L1420F, S1691R, V2424G), and a single silent mutation (P1526P) that was more common in cases than controls from a small breast cancer study. In preliminary logistic regression analyses, 11 of the variants have been tested in 830 breast cancer cases and 859 controls frequency matched on year of birth. The same number of cases and controls (n=3 each, 0.35%) carry at least one of the rare protein-truncating/splicing mutations analyzed thus far, although four variants (IVS10-6G>T,1563delAG, K1192K, and 7636del9) are yet to be completed. The only missense mutation analyzed thus far associated with breast cancer is S49C (TCC>TGC), present in 3.7% of cases and 2.2% of controls (OR = 1.71, 95% C.L. 0.96 – 3.04). Unlike a previous study, the P1526P (CCC>CCT) polymorphism was significantly less common in cases (6.5%) than controls (11.0%), OR = 0.56, 95% C.L. 0.38 – 0.90. Adjustment for race/ethnicity or known breast cancer risk factors did not alter the point estimates appreciably. Additional laboratory and statistical analyses continue, but other than the S49C and P1526P polymorphisms, no significant differences in AT-causing *ATM* mutations or non-conservative missense polymorphisms have been observed between breast cancer cases and controls. When our ongoing occupational radiation dose assessment is completed, we will evaluate whether radiation associated breast cancer risks are modified by *ATM* genotype.

**#C93 A Pooled Analysis of DNA Repair Polymorphisms and Head and Neck Cancer Risk.** Wen-Yi Huang,[1] Andrew F. Olshan,[2] Stephen M. Schwartz,[3] Sonja I. Berndt,[1] Chen Chu,[3] Richard B. Hayes.[1] NIH-NCI-DCEG,[1] Bethesda, MD, University of North Carolina at Chapel Hill,[2] Chapel Hill, NC, Fred Hutchinson Cancer Research Center,[3] Seattle, WA.

**Background:** Tobacco and alcohol consumption are major risk factors for head and neck cancer, likely due to their DNA-damaging metabolites. Genetic variation in DNA repair capacity may modify the risk of head and neck cancer. **Methods:** Using data and DNA specimens from case-control studies in western Washington State, North Carolina, and Puerto Rico totaling 555 cancer cases and 792 controls, we studied the risk of head and neck cancer in relation to genetic polymorphisms in DNA repair genes. In a single lab, we assayed for common nonsynonymous polymorphisms in XRCC1 (Arg399Gln) and XPD (Lys751Gln), previously reported to be associated with risk of head and neck cancer, and in MGMT (Ile143Val and Leu84Phe), and XRCC3 (Thr241Met). Multivariate logistic regression analysis using pooled data was performed to calculate odds ratios (OR) and 95% confidence intervals (CI), adjusting for gender, race, age, cigarette smoking, alcohol, and study center using a random-effects model. **Results:** The distributions of all studied genotypes were consistent with Hardy-Weinberg equilibrium among controls for whites (n = 695), blacks (n = 46), and other racial groups (n = 51). Genotype-associated head and neck cancer risks were similar across all three studies for all studied polymorphisms except XPD751 (p for heterogeneity = 0.06 among whites). In pooled analyses among all subjects and among whites only, carriage of the MGMT 143Val (minor) allele (vs. 143Ilelle) and the MGMT 84Phe (minor) allele (vs. 84LeuLeu) was associated with decreased risks of head and neck cancer (OR = 0.7, 95% CI = 0.5-0.9 and OR = 0.7, 95% CI = 0.5-1.0, respectively, among whites). XRCC1 399GlnGln (vs. 399ArgArg) was also associated with a decreased risk of head and neck cancer (OR = 0.6, 95% CI = 0.3-0.9, among whites). XPD-751 and XRCC3-241 were not independently associated with risk. Considering joint effects with the two major risk factors for head and neck cancer, alcohol-related risks tended to be more pronounced among MGMT 143Ilelle, XRCC3 241ThrThr, and XPD 751LysLys homozygotes (p for interaction = 0.1, 0.01, and 0.09, respectively), while no modification of smoking-related risks were found. **Conclusion:** Pooled data from three case-control studies suggest that DNA repair enzymes may play a role in head and neck carcinogenesis, particularly by modifying the risk associated with alcohol consumption.